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14. ABSTRACT The Foundation Fighting Blindness Clinical Research Institute (FFB CRI) [formerly National Neurovision Research Institute (NNRI)], the clinical arm of the Foundation Fighting Blindness (FFB), established the National Eye Evaluation Research (NEER) Network, composed of collaborative group of five Clinical Treatment and Evaluation Center (CTECs). The intent of this Network was to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research carried out encompassed; (i) a Phase II clinical trial to evaluate the safety and efficacy of new therapeutic and preventive approaches, by repurposing an FDA-approved small molecule drug; (ii) natural history studies to develop standardized criteria to define disease stage, severity and progression; (iii) observational studies to enhance understanding of the natural history of these diseases for different genotypes and phenotypes; and (iv) evaluations of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions.

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Introduction:

The Foundation Fighting Blindness Clinical Research Institute (FFB CRI), the clinical arm of the Foundation Fighting Blindness (FFB), established the National Eye Evaluation Research (NEER) Network composed of a collaborative group of five Clinical Treatment and Evaluation Centers (CTECs) and a two support groups- the Clinical Coordinating Center and an independent visual image reading center. The intent of this Network remained the same throughout the award period as in the original application: to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD) through the conduct of clinical trials and other clinically relevant research. The scope of research carried out encompassed:

- A Phase II clinical trial to evaluate the safety and efficacy of a new therapeutic and preventive approaches, by repurposing an FDA-approved small molecule drug
- Natural history studies to develop standardized criteria to define disease stage, severity and progression;
- Observational studies to enhance understanding of the natural history of these diseases for different genotypes and phenotypes; and
- Evaluation of the reliability and validity of different available treatment outcomes measures to determine those that are most appropriate for various genotypes and phenotypes as well as for specific interventions.

The NEER Network devised standard protocols for data collection, maintained and expanded standardized patient databases, classified by patient genotype and phenotype, to allow for the timely identification of eligible patients and facilitate patient access for clinical trial participation. In addition, the NEER network maintained readiness to collaborate with the Department of Defense, training programs for military ophthalmologists in the latest technologies and diagnostic and treatment regimens. An important reason for the development of the NEER network was that military populations mirror the civilian population, including for the incidence of retinal diseases. Soldiers and their families therefore suffer from the same sight-robbing retinal degenerative diseases as the general population. In addition, the military's expanding retiree population will suffer from age-related macular degeneration (AMD) and useful preventative or treatment regimen information will greatly enhance these persons' lives by preventing them from losing vision.

The NEER network, in cooperation with COL Donald A. Gagliano, MD, MHA, DOD, Principal Advisor for Vision, Director, DODNA Vision Center of Excellence, and others in DOD, as appropriate, intended to develop a program to include military hospitals and ophthalmologists in clinical trials for Retinal Degenerative Diseases so that military personnel and their families will directly benefit from the new preventions, treatments and cures for these sight robbing diseases. Also, the NEER network planned to work with the appropriate military office to develop a fellowship and senior physician training and continuing education program for military ophthalmologists to obtain specialized training at NEER network academic centers in the latest technologies, including non-invasive imaging such as multifocal electroretinogram (mfERG), optical coherence tomography (OCT), and Adaptive Optic Scanning Laser Ophthalmoscopes (AOSLO). Unfortunately, despite ongoing readiness of the NEER network, circumstances necessitated that our DOD partners devote their time to other endeavors.

Body:

The Foundation Fighting Blindness Clinical Research Institute (FFB CRI), the clinical arm of the Foundation Fighting Blindness (FFB), established the National Eye Evaluation Research (NEER) Network, which is composed of a collaborative core group of five (5) Clinical Treatment and Evaluation Centers (CTECs). The intent of the NEER Network was to advance the science of therapeutic and preventive interventions for inherited orphan retinal degenerative diseases and dry age-related macular degeneration (AMD). This was accomplished within the NEER Network through the conduct of clinical trials and other clinically relevant studies. Pertinent background information on the FFB, the FFB CRI, the retinal diseases to be studies, and the rationale underlying the need for and feasibility of this new Network are delineated below.

The Foundation Fighting Blindness is the world's largest source of non-governmental support for research on inherited orphan retinal degenerative diseases and dry AMD. Since its inception in 1971, the Foundation has raised more than $550 million and, in the current fiscal year, is providing over $21 million in funding for 138 grants, including Research Centers. The research projects of these grants are conducted by 190 research investigators at 73 Institutions, Eye Hospitals and Universities. In addition to funding researchers within the United States, FFB funding extends internationally including laboratories in Canada, England, France, Germany, Italy, Israel, China, and the Netherlands.

To promote collaborations between basic and clinical researchers and accelerate the advancement of promising preventive and therapeutic approaches to the clinic, the Foundation also supports Research Centers internationally. The Research Center Program involves inter-disciplinary groups of investigators conducting multiple research projects with an emphasis on translational research to facilitate clinical applications and the sharing of research tools, knowledge and data.

In 2003, the Foundation established the FFB CRI (formerly known as the National Neurovision Research Institute or NNRI), a non-profit entity, to capitalize on the fairly recent emergence of therapeutic and preventive products and devices that require rigorous clinical evaluation for safety and efficacy. The mission of the FFB CRI is to accelerate the translation of promising research on treatment and prevention approaches into clinical trials. On July 1, 2012, the FFB CRI was renamed from NNRI to the Foundation Fighting Blindness Clinical Research Institute (FFB CRI) in order to provide a better message that reinforces the link between FFB CRI and the Foundation Fighting Blindness.

Inherited orphan retinal degenerative diseases are a family of inherited pathologies with the ultimate consequence of photoreceptor death and severe visual impairment usually ending in blindness. In the United States, the total number of individuals affected by retinitis pigmentosa (RP) and other forms of rare inherited retinal degenerative diseases is estimated at approximately 200,000 individuals. RP, Stargardt disease, and Usher syndrome represent the predominant forms of inherited orphan retinal degenerative diseases and are estimated to affect -80,000 -100,000, -25,000, and -20,000 individuals in the U.S., respectively. Genetic heterogeneity is a key feature of each of these predominant diseases. To date, over 200 genes with mutations causing one or more forms of inherited orphan retinal degenerative diseases have been cloned, and over 50 more have been identified based on candidate gene studies or linkage mapping.

In the majority of inherited orphan retinal degenerative diseases, visual impairment is detected in the first or second decade of life. Assuming that 30% of individuals will reach legal blindness by their third decade of life, 30% by the fourth decade of life, 30% by the fifth decade of life, while 10% never reach legal blindness, and considering just the annual cost of blindness to the U.S. government, adjusted annually for inflation at a rate of 2.5%, then the cumulative minimal lifetime costs incurred by the U.S. government for the current civilian and military populations affected by inherited orphan retinal degenerative diseases is more than $38 billion. This tremendous economic burden will not only continue to be incurred, but will increase unless efforts are made to define the molecular, biochemical and clinical parameters of these diseases and to

advance capabilities to a point where rational, safe therapeutic strategies can be designed, tested and adopted as standard care.

While repeat evaluation and study of affected patients are vital to rigorously characterize the unique features of various diseases and the factors that cause disease progression, several obstacles in addition to the lack of research funding, often prevent the necessary frequency and thoroughness of patient examination. First, patients are often diagnosed by ophthalmologists who have limited training in the diagnosis and management of patients with rare forms of inherited orphan retinal degenerative diseases. Second, once patients are informed of the current lack of treatment options for their disease condition, they have little incentive for engaging in repeat clinical evaluations. Third, and perhaps more rare than the diseases themselves, is the number of clinicians fully trained in both the clinical and genetic aspects of inherited orphan retinal degenerative diseases. Training of additional clinical specialists in diagnostic and genetic evaluation of patients with rare forms of inherited retinal degenerative diseases has been identified as one of the most important resources needed to ensure that therapies for these diseases reach the clinic.

Despite inherited orphan retinal degenerative diseases accounting for a small portion of all vision loss, dry age-related macular degeneration accounts for approximately 90 percent of all age-related macular degeneration (AMD), affecting over 7 million individuals in the United States alone. With dry AMD yellow-white deposits composed of waste products from photoreceptor cells, called drusen, accumulate in the retinal pigment epithelium (RPE) tissue beneath the macula. The RPE tissue can lose its ability to process waste and drusen deposits accumulate in the RPE, reasons for this are being investigated with FFB support. These deposits are thought to interfere with the function of photoreceptors and the RPE in the macula, causing progressive degeneration of these cells with the eventual loss of vision.

Vision loss from dry AMD occurs very gradually over the course of many years. Central vision may even remain stable between annual eye examinations, and individuals with dry AMD do not usually experience a total loss of central vision. However, vision loss may make it difficult to perform tasks that require finely focused vision (e.g., driving or reading). Although there are extensive research efforts underway to identify treatments for dry AMD, at this time the only proven treatment for late-stage drug AMD is the Age-Related Eye Disease Study (AREDS) antioxidant supplement regimen, stopping smoking, and eating healthfully.

Through the research programs conducted with the support of the FFB and, more recently, through the FFB CRI, and the National Eye Institute of the National Institutes of Health (NIH), basic scientific discoveries have shown that selected nutritional factors, neuroprotective drugs, and gene therapies are safe and can prevent visual loss or restore visual function in preclinical animal models of certain genetically defined forms of inherited orphan retinal degenerative disease and dry AMD. While AREDS antioxidant formulation is a widely accepted treatment, clinical trials of other potentially more effective treatments are imminent.

Recent progress in the classification of mutations for various inherited orphan retinal degeneration and dry AMD genotypes and the development of treatment possibilities raise the likelihood that potential treatments will be ready for evaluation in clinical trials in the near future. Unfortunately, there are considerable obstacles to the successful conduct of these clinical trials, including:

- Lack of resources for the design and conduct of effective and efficient clinical trials for inherited orphan retinal degenerative diseases and dry AMD;
- Limited number and wide geographic distribution of potentially eligible patients across the U.S., making follow up examinations at one clinical center financially and logistically problematic, if not unfeasible;
- Limited number of retinal specialists with expertise in these diseases;

- Use of diverse, non-uniform approaches to measuring disease severity, stage and progression; and
- Unresolved methodologic issues, such as determination of clinically meaningful, reliable and valid outcome measures.

The development of a clinical trials network has shown its efficacy in being an efficient and valuable approach to overcome these obstacles and to maximize the resources currently available (see report below on the ongoing VPA clinical trial in the NEER network for autosomal dominant retinitis pigmentosa, and the ProgSTAR studies for Stargardt disease). As new interventions become available for clinical evaluation, the creation of the network will continue to provide the infrastructure necessary to facilitate the initiation and conduct of properly designed clinical trials of investigational therapeutic and preventive approaches and devices in a timely manner. The development of the clinical trials network in inherited orphan retinal degenerations and dry AMD required the cooperation of an interdisciplinary team with clinical, genetic, and basic science expertise.

Key Research Accomplishments:

[NOTE: In 2010, the FFB CRI worked with TATRC to apportion its two grants (-0189 and -0720) into consistent expense categories. Previously, it had been submitted and approved by TATRC that the -0189 grant would support the NEER infrastructure while the -0720 grant would support the actual clinical trial and natural history studies, including CTEC costs associated with these functions. This final report for grant -0189 demonstrates the support of the overall operation of the NEER network, as well as support to ongoing clinical efforts.]

NEER's first clinical trial (VPA Study) continues to progress and is anticipated to complete full enrollment in August 2014. The 6 clinical sites:

- Retina Foundation of the Southwest,
- *Moran Eye Center at the University of Utah
- Bascom Palmer Institute at the University of Miami
- Hamilton Eye Institute at the University of Tennessee
- Casey Eye Institute at the Oregon Health & Science University
- Kellogg Eye Center at the University of Michigan Ann Arbor

***CTEC Center**

have all actively screened and enrolled study participants. Data from the VPA study has been leveraged for an additional analysis entitled the EZ Area study.

NEER's ProgSTAR-1 and ProgSTAR-2 studies examine, prospectively and retrospectively, the natural history of the progression of Stargardt's disease. The study has completed all start-up procedures. The protocols' enrollment goals are to enroll 150 to 250 patients by the end of 2014. The ProgSTAR-1 protocol has currently enrolled 119 patients and the ProgSTAR-2 protocol has currently enrolled 178 patients. The 9 institutions involved with the ProgSTAR protocols include:

- *Wilmer Eye Institute at the Johns Hopkins University
- Greater Baltimore Medical Center
- Scheie Eye Institute at the University of Pennsylvania
- Cole Eye Institute at the Cleveland Clinic
- *Moran Eye Center at the University of Utah
- Retina Foundation of the Southwest
- University of Tuebingen, in Tuebingen, Germany
- The Vision Institute, in Paris, France
- Moorfields Eye Hospital, London, United Kingdom

*CTEC Center

The FFB patient registry (named "My Retina Tracker") has been developed and ongoing refinements of the interactive computerized patient registry continue. The programming has been thoroughly tested to ensure that the adaptive programs used by people with low visual function will operate properly. Clinical and Researcher portals are under development. Patient enrollment (currently 475 patients) is ongoing.

Details

VPA Study:

The six clinical sites are finalizing efforts to reach the study goal of randomizing 90 subjects. One hundred and eighty-seven subjects have been screened, 85 subjects have been randomized, 7 potential subjects are currently awaiting randomization, 6 subjects have been prescreened and 40 subjects have completed the study. Enrollment is expected to complete by the end of August 2014.

The EZ area study, leveraging data already collected from the VPA study, shows some potential to demonstrate measureable and meaningful changes to the retina in retinitis pigmentosa. The 'EZ' in EZ area refers to the 'ellipsoid zone' or the edge of the area of retinal degeneration in the retina as visualized by images collected by OCT (optical coherence tomography); OCT is a widely available, quick, and minimal risk imaging technique. EZ-Area refers to the total calculated measurable Area of the central retina that has not yet undergone degeneration. FFB CRI plans to meet with FDA and present EZ area as a potential validated endpoint as part of a new pharmaceutical intervention project.

Over the past year, the FFB CRI Data Safety Monitoring Board (DSMB) met face to face in November 2013 and by teleconference in April 2014. The DSMB reviewed all of the VPA study safety data and recommended that the VPA study continue without any change to the protocol.

ProgSTAR Study:

As described in previous Quarterly and Annual Reports, FFB CRI explored the feasibility of conducting a hybrid retrospective/prospective Natural History study of individuals affected with Stargardt's disease. The NEER CTEC site at Wilmer Eye Institute at the Johns Hopkins Hospital has been instrumental in providing expertise for this study, and is the project scientific lead as well as a clinical site. The NEER CTEC site at the Moran Eye Center at the University of Utah is also participating as one of the clinical sites. Both domestic and European (UK, France, Germany) clinical sites are involved with this study in order to collect an adequate volume of data regarding disease progression from individuals affected by this rare, orphan, inherited retinal degenerative disease. The previously reported 2012 feasibility study indicated that the 9 identified potential clinical sites have adequate facilities and patients to complete recruitment within estimated project timelines.

The data collection for the ProgSTAR study utilizes a secure, online electronic case report form system coordinated by the Dana Center for Preventative Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University; the study reading center is the Doheny Institute affiliated with the University of Southern California. Both the Dana Center and the Doheny Institute are very experienced ophthalmic research organizations.

A total of 119 subjects have been enrolled into the ProgSTAR-1 protocol and 178 subjects have signed the consent to participate in the ProgSTAR-2 retrospective data review protocol; patient visits are ongoing.

Site IRB approval status is summarized below:

Site	Prospective	Retrospective
Johns Hopkins	**APPROVED**	**APPROVED**
GBMC	**APPROVED**	**APPROVED**
RFSW	**APPROVED**	**APPROVED**

UPENN	**APPROVED**	**APPROVED**
Utah	**APPROVED**	**APPROVED**
Cleveland	**APPROVED**	**APPROVED**
UK	**APPROVED**	**APPROVED**
Paris	**APPROVED**	**APPROVED**
Germany	**APPROVED**	**APPROVED**

The subsequent HRPO review status is summarized below:

Site	Prospective	Retrospective
Johns Hopkins	**APPROVED 7/24**	**APPROVED 9/23**
GBMC	**APPROVED 7/17**	**APPROVED 7/17**
RFSW	**APPROVED 10/7**	**APPROVED 9/23**
UPENN	**APPROVED 9/5**	**APPROVED 7/17**
Utah	**APPROVED 12/5**	**APPROVED 9/5**
Cleveland	**APPROVED 11/25**	**APPROVED 9/5**
UK	**APPROVED 12/5**	**APPROVED 9/5**
Paris	**Withdrawn***	**Withdrawn***
Germany	**APPROVED 9/30**	**APPROVED 10/11**

*The Paris site withdrew from status as a DOD-supported site due to time restrictions for site start-up in order to meet all DOD requirements.

FFB CRI Patient Registry:
FFB CRI completed the development of the infrastructure and programming for a new web-based patient registry of individuals affected by inherited retinal degenerative diseases. FFB CRI has affiliated the registry with the NIH Office of Rare Diseases Research (ORDR) and has joined the effort of the Global Rare Diseases Patient Registry and Data Repository (GRDR) to collect patient clinical information without any personal identifiers (de-identified information), for clinical research. The FFB registry will be accessible and interactive for patients and has been named "My Retina Tracker". The protocol for the registry has received NEER network central IRB (Western IRB) approval and has been approved by HRPO.

The registry has been released and available to interested individuals in order; active adjustments to the programming for compatibility with adaptive programs that are used by people with low visual function continue.

Training Program for DOD Ophthalmologists:
FFB CRI made initial preparations to develop an education program for inherited retinal degenerative diseases for the benefit of military Ophthalmologists through the DOD's Vision Center of Excellence. The Vision Center of Excellence was working on other initiatives during the award period and FFB CRI was unable to partner in any education program collaborations.

Reportable Outcomes:
Manuscripts: None until the supported VPA, ProgSTAR and EZ Area studies are completed and all data analyzed

Abstracts: None

Presentations:

- ProgSTAR was presented at the University of Pennsylvania Vision Colloquium, University of Pennsylvania, Philadelphia, November 5,2012

- ProgSTAR was presented twice at the Deutsche Ophthalmologische Gesellschaft (DOG) Meeting in Berlin
    - SA55-367 A state-of-the-art in SD-OCT: Retinal morphology relevant for retinal disease; Hendrik Scholl (Baltimore/USA)
    - SA72-483 Genetics of the visual cycle- consequences for supplementation and therapy Genetik des Vitamin A-Zyklus- Konsequenzen fur Nahrungserganzung und Therapie; Hendrik Scholl (Baltimore/USA)
- ProgSTAR was presented at the 2012 Retina Society Meeting: RET IRD 01 trial
- ProgSTAR was presented at the AAO meeting in Chicago, November 12, 2012
- ProgSTAR was presented at the Association for Vision and Ophthalmology (ARVO) in Seattle, WA, May 2013
- ProgSTAR was presented at the Retinal Gene Therapy Conference in Portland, OR May 2013
- EZ Area poster was presented at the Association for Vision and Ophthalmology (ARVO) in Orlando, FL, May 2014
- ProgSTAR was presented at the VISIONS 2014 conference in Colorado, June 2014

Patents and licenses applied for and/or issued: None

Degrees obtained that are supported by this award: None

Development of cell lines, tissue or serum repositories: None

Informatics and Databases: Developed for the ProgSTAR study and VPA study (VPA study database successfully utilized for EZ Area study)

Animal Models: None

Funding applied for based on work supported by this award: None

Employment or research opportunities applied for and/or received based on experience/training supported by this award: None

Conclusion:

All CTECs continue to be available for NEER participation and have completed their NEER/FFB CRI establishment contracts. In addition, the FFB CRI has fully implemented infrastructure for the network: an identified pool of experienced clinical research sites, EMMES as the NEER Network Clinical Coordinating Center (NNCCC), the Translational Clinical Trials Center (TCTC) at the Casey Eye Institute, Oregon Health and Science University (OHSU) as the independent image Reading Center, and WIRB as the IRB of record for the NEER Network. FFB CRI plans to continue to convene working groups of clinicians to define clinical trial parameters for inclusion/exclusion and endpoints for clinical trials in inherited retinal degenerations.

FFB CRI plans to continue the work begun during the period of award support, i.e., to work with both academic investigators and biotech companies on very promising leads for potential additional opportunities for the NEER network. It is anticipated that during the upcoming year, all of the NEER network active clinical trials (one clinical and two natural history protocols) will complete enrollment and follow-up study visits.

FFBCRI Data and Safety Monitoring Board Meeting
VP1 Study
Wednesday, October 2, 2013
12:00 PM – 3:30 PM ET

OPEN SESSION WITH ACTION ITEMS AND RECOMMENDATIONS

List of Attendees:

Data and Safety Monitoring Board (DSMB)	Stuart Fine, MD, Chair Gary Ingenito, MD, PhD Jacque Duncan, MD Dean Bok, PhD Marie Diener-West, PhD Karen Rothenberg, JD
Foundation Fighting Blindness (FFB)	Stephen Rose, PhD
Foundation Fighting Blindness Clinical Research Institute (FFBCRI)	Judith Chiostri, MS
Clinical Coordinating Center (CCC)	Nilay Shah, MD Paul VanVeldhuisen, PhD Jennifer McCormack, MS Aimee Wahle, MS Maria Figueroa, MBA

The meeting opened with an executive closed session of the DSMB with Dr. Rose also in attendance. After the executive session, staff from the Clinical Coordinating Center and Foundation Fighting Blindness Clinical Research Institute joined the DSMB for an open session. The open session was followed by a closed session of the DSMB, and the meeting ended with another executive closed session with Dr. Rose in attendance. Minutes of the closed sessions are provided in a separate document accessible only to DSMB members and unmasked staff from the CCC and FFB.

Below is a list of recommendations and action items based on discussions in both the open and the closed sessions, followed by the meeting minutes of the open session.

Recommendations:

1. The DSMB recommends the continuation of the VP1 study.
2. Clinical sites should continue to emphasize recruitment especially with respect to those with RHO mutations because those participants seem to be most likely to respond to VPA.
3. The DSMB does not recommend an interim analysis of futility as recruitment is nearing completion, nor do they recommend a RHO subgroup analysis at this time, but instead recommend performing this RHO subgroup analysis at the time of the final analysis after data lock.
4. The DSMB appreciated being informed about the EZ area project and how the OCT measures in this trial are being utilized to possibly validate a new clinical endpoint. Although the presentation was strictly informational, the DSMB is interested in being informed about the progress of this ancillary study.
5. The DSMB requests that percent change from baseline for visual field measures be included in the closed session report in addition to absolute change from baseline.

Action Items:

1. Dr. Rose will provide the publication on the use of color contrast thresholds in RP to the DSMB.
2. FFBCRI will update the DSMB on the progress of the EZ area working group at the next DSMB meeting.

3. A number of changes to the presentation of data in the DSMB report were requested of the CCC. These include:
    a. Add the number who completed 52 weeks of treatment to the summary of participant disposition in the open and closed session reports.
    b. Include a summary table of the distribution of genotypes by treatment arm for the closed session report.
    c. Add percent change from baseline to the efficacy summary tables in the closed session report.
    d. Include a breakdown of the efficacy endpoints by treatment arm within site in the closed session report.
    e. Present baseline results for the subgroup of participants who also have week 52 results.
    f. Provide a more detailed explanation of the box plots of the efficacy endpoints in the closed session report.
4. The CCC will provide the DSMB with information on quality control procedures at the Reading Center.
6. FFBCRI will schedule the next meeting as a teleconference on either April 7, 8, or 9, 2014. FFBCRI will circulate a poll to identify the date and time the teleconference will occur.

Open Session

Ms. Chiostri provided an update on enrollment for the VP1 study. As of the date of the meeting, there are 71 participants randomized and 15 participants in screening, with approximately 15 potential participants identified for screening. Forty-eight percent of the 71 randomized participants have RHO mutations. Ms. Chiostri noted that randomization slowed down in the summer, in part due to a higher than average number of participants unwilling to delay childbearing at the Miami site. She stated that the goal remains to complete recruitment by December 2013. Ms. Chiostri reported that the study is within the budget and contingency funds are available to extend enrollment a by a few months if necessary.

Ms. McCormack reviewed the recommendations and action items from the May 15, 2013 DSMB meeting. All action items were completed. She noted that sites were not told to focus recruitment on participants with RHO mutations. Professor Rothenberg questioned why the decision to not follow the DSMB recommendation was made. Ms. Chiostri replied that the FFBCRI Board decided not to impose this limitation on recruitment because they would like to finish enrollment as soon as possible. Ms. McCormack reported that the Informed Consent was updated with the information from the FDA warning letter recommending that VPA not be used in pregnant women for migraine prevention.

Dr. Duncan provided an overview of Dr. Birch's work on the new clinical endpoint EZ area, and explained that data from the VP1 study can be used as a basis to validate this measure. Dr. Duncan provided a description of the ellipsoid zone (referred to as EZ) area measurement, which is the distance calculated from spectral domain OCT scans between the edge (i.e., the inner segment/outer segment) of the advancing RP degeneration on either side of the fovea. She stated that the EZ area is an objective structural measure that may correlate well with functional measures of visual field, and because it has less variability than functional measures of visual field and is easier to measure, it could be an important outcome measure to predict progression of RP in clinical trials. Dr. Duncan noted that data from the VP1 study provides a unique opportunity to validate the EZ area measurement. The group reviewed some additional slides provided by Dr. Birch from his recent publication on this topic.

Dr. Duncan reported that there is currently a working group underway to determine if EZ area could be used as the primary endpoint in clinical trials. Dr. VanVeldhuisen provided more information on the working group, of which he is a member. He noted that the end goal is to meet with the FDA to discuss EZ area as an acceptable primary outcome measure in RP studies, using data collected in the VP1 study as a basis for that goal. Professor Rothenberg inquired about the effect of validating the EZ area endpoint in the VP1 study. Dr. Rose, Dr. Diener-West, and Dr. VanVeldhuisen all stated that there would be no impact on the VP1 study, as this is secondary analysis of data already collected and requires no additional information from study participants. Dr. Fine asked whether FFB had any concerns about Dr. Francis's participation in the working group, and Dr. Rose responded that FFB is comfortable working with him. Professor Rothenberg questioned whether there was any conflict of interests in the validation of the EZ area endpoint, as Dr Birch from the

working group is also an investigator in the VP1 study. After discussion, the board did not believe there was concern on this issue.

Dr. Fine asked the DSMB members to comment upon the proposed RHO subgroup analysis and interim analysis. Dr. Diener-West stated that she was against performing the RHO subgroup analysis at this time due to the small number of participants with week 52 data and the possibility that its performance may be viewed negatively by reviewers of the study manuscript, consistent with the RHO subgroup analysis proposal provided by the CCC. Dr. Diener-West recommended that the RHO subgroup analysis instead be performed at the time of final analysis after data lock. She also stated that there was no point in performing an interim analysis now that recruitment is nearing completion. Professor Rothenberg agreed with Dr. Diener-West's views. Dr. Fine inquired if any DSMB members disagreed with this plan of action, and no DSMB members had any issues following Dr. Diener-West's recommendations.

Ms. McCormack provided a presentation of the masked data from the VP1 study. She noted that the number of participants refusing to participate due to transportation issues has decreased due to the additional funding provided to sites by FFBCRI (Table 2). There were 8 participants declining participation due to transportation issues in May and June, and none since July. Ms. McCormack next presented information on participant disposition included in Table 4. Dr. Duncan requested that the number of participants completing 52 weeks of treatment be added to this table. Ms. McCormack provided an overview of demographic information found in Table 5 and noted that 19% of participants are females of childbearing potential, and the mean age of participants is 51 years.

Ms. McCormack presented data on the distribution of genetic mutations (Table 12) and noted that 47% participants of the 70 participants in the data freeze have RHO mutations. Dr. Duncan inquired if the two participants with both a RHO mutation and a PRPH2 mutation could be considered part of the RHO subgroup. Dr. Bok replied that those two participants could potentially be included in the RHO subgroup, but members suggested that since there were only two participants, that it may be best to keep the RHO subgroup analysis limited to those with only a RHO mutation and exclude these two participants from the analysis. It was noted that these two participants who were enrolled at the Miami site are believed to be siblings. Dr. Diener-West stated that she is beginning to be concerned about the correlation that may exist in the data due to multiple sets of related participants. Ms. McCormack replied that capturing this information in the study database had been considered, but it was decided not to pursue this issue due to potential privacy issues. It is thought this information on relationship of participants could be obtained from the sites if needed.

Ms. McCormack provided a description of data on treatment exposure and compliance included in Tables 15, 16, and 17 and Figure 2. She noted that 15% of participants had treatment exposure below 90%. Dr. Duncan inquired about the two participants with treatment exposure over 100%. Ms. McCormack responded that one participant did not return pills at a visit, and this problem should resolve itself in the future once the pills unaccounted for are returned. The other participant took a higher dose than what was instructed. Professor Rothenberg questioned if any participants did not take study drug due to adverse events, and Ms. McCormack replied that this had occurred. Dr. Ingenito suggested that a per-protocol analysis could be restricted to include only participants above a certain level of treatment exposure. He then inquired about the proposed analysis method to account for missing data. Ms. McCormack noted that the statistical model will take missing data into account, and Dr. VanVeldhuisen stated that multiple imputation and LOCF are being considered. The statistical analysis plan has not yet been finalized.

Ms. McCormack discussed the safety data for the VP1 study. She noted that five serious adverse events have occurred, including a death from a motorcycle accident. Ms. McCormack stated that none of the criteria for stopping the study had been met. She noted that there were five clinically significant elevated liver function tests and three clinically significant elevated pancreatic function tests. Ms. McCormack reported that in general there are no particular concerns from the medical/safety monitors. Dr. Shah stated that the CCC is currently following up with sites about high lipase values, and overall there were no trends in adverse events. Professor Rothenberg noted that nausea and headache were the most common adverse events, which is to be expected. Dr. Shah discussed the participant death due to the motorcycle accident and noted that the site currently considers the death related to study product, but the CCC Medical Monitor and FFBCRI disagree with that designation and will not be reporting this serious adverse event to the FDA, unless further information is obtained that indicates otherwise.

Ms. McCormack provided a brief description on the data quality of the VP1 study and noted that sites are doing well at submitting data in a timely and accurate manner. She reported that most missed visits were telephone

visits (Table 22), and there are only a small percentage of missing forms (Table 23) and missing values (Table 24). Ms. McCormack noted that there was a 1.43% error rate at all data audits across all sites.

The next DSMB meeting will be scheduled as a teleconference in April 2014.

FFBCRI Data and Safety Monitoring Board Meeting
VP1 Study
Wednesday, April 30, 2014
10:00 AM – 12:00 PM ET
OPEN SESSION WITH ACTION ITEMS AND RECOMMENDATIONS
List of Attendees:

Data and Safety Monitoring Board (DSMB)	Stuart Fine, MD, Chair Gary Ingenito, MD, PhD Jacque Duncan, MD Dean Bok, PhD Marie Diener-West, PhD Karen Rothenberg, JD, MPA
Foundation Fighting Blindness (FFB)	Stephen Rose, PhD
Foundation Fighting Blindness Clinical Research Institute (FFBCRI)	Patricia Zilliox, PhD Judith Chiostri, MS
Clinical Coordinating Center (CCC)	Robert Lindblad, MD Nilay Shah, MD Paul VanVeldhuisen, PhD Jennifer McCormack, MS Aimee Wahle, MS Janet Van Dyke
TCTC Reading Center	David Wilson, MD

The meeting opened with an executive closed session of the DSMB with Dr. Rose also in attendance. After the executive session, staff from the Clinical Coordinating Center and Foundation Fighting Blindness Clinical Research Institute joined the DSMB for an open session. The open session was followed by a closed session of the DSMB, and the meeting ended with another executive closed session with Dr. Rose in attendance. Minutes of the closed sessions are provided in a separate document accessible only to DSMB members and unmasked staff from the CCC and FFB.

Below is a list of recommendations and action items based on discussions in both the open and the closed sessions, followed by the meeting minutes of the open session.

Recommendations:

1. There were no safety concerns that would warrant early termination of the trial.
2. Continuation of the VP1 study and recruitment of eligible participants through August 31, 2014 after which time no further participants should be recruited. All participants should be followed for 52 weeks from date of randomization for their primary outcome and 65 weeks for their safety visit.
3. Sites should continue to focus on enrolling eligible participants through August 31, 2014, particularly those who are in the pre-screening and screening process.

Action Items:

1. FFBCRI will provide the ARVO EZ area poster to the DSMB.
2. FFBCRI will provide enrollment metrics for retinal degenerative disease studies and glaucoma studies to the DSMB.
3. FFBCRI will schedule the next meeting on October 1, 2014 from noon to 4 pm ET in Columbia, MD.

<u>Open Session</u>

Dr. Zilliox provided an update on enrollment for the VP1 study, noting that there are currently 83 participants enrolled. She reported that the FFB board has provided additional funding to extend enrollment in order to achieve 90 participants, and agreed that no interim analysis should be conducted. She noted that Dr. Goldberg recently sent a letter to the sites to encourage enrollment. Dr. Zilliox commented that it has been difficult to find participants, and in retrospect, there should have been at least 10 sites involved in the study. She noted that enrollment per month in the VP1 study is similar or better than the enrollment rate in other retinal degenerative diseases and glaucoma studies. Dr. Zilliox indicated that FFBCRI will provide the DSMB with the recruitment information for these other retinal degenerative diseases and glaucoma studies. She also noted that GeneDx is expediting genotyping.

Dr. Zilliox provided the board with an update on the new clinical endpoint ellipsoid zone (EZ) area. She stated that the goal is to use Dr. David Birch's work and the data from the VP1 trial to validate the EZ area endpoint. She noted that there is an ARVO poster on the baseline correlations between EZ area and visual field measures, and indicated that she will provide the poster to the DSMB. Dr. Zilliox reported that FFBCRI has been in discussions with several companies interested in using EZ area as an endpoint for a RP clinical trial. BIKAM has agreed to move forward with submitting a pre-IND package to the FDA to conduct a trial with a molecular chaperone for adRP using EZ area as the endpoint.

Dr. Duncan inquired if the data from the 83 participants currently enrolled in the VP1 study would be sufficient to validate the EZ area endpoint. Dr. Zilliox responded that although the idea is to maximize the amount of information obtained, she believed that the additional 7 participants may not add that much to the analysis. She explained that EZ area cannot be measured early in the disease progression and noted that approximately half of the VP1 participants looked at thus far were able to have EZ area measured. Dr. VanVeldhuisen was in agreement, and indicated that it is hard to know at this time if the data from the VP1 study would be sufficient to validate EZ area. He noted that some correlation between baseline visual field and EZ area has been observed.

Dr. Diener-West questioned if there is a plan to change the primary endpoint of the VP1 study to EZ area. Dr. VanVeldhuisen responded that there will be no change to the primary endpoint. He stated that the analysis of EZ area in the VP1 study would be exploratory. He also noted that the EZ area endpoint could be measured in only half of the participants.

Dr. Zilliox pointed out that one benefit of the VP1 study has been the identification of a cohort of six clinical sites for future studies. Dr. Duncan agreed, and encouraged FFBCRI to continue to identify other sites due to the difficulty in recruitment for the VP1 study. Dr. Zilliox responded that there have been discussions about a registry of RP patients. She explained that in the discussions with several companies about the EZ area endpoint, they learned that many of those companies are also planning RP studies, and she noted that that FFBCRI would be competing with them to enroll participants.

Ms. Chiostri provided an update on enrollment. She reported that as April 29, 2014, there are a total of 83 participants randomized, an additional 6 potential participants active in the screening process, and an additional 10 potential participants who have been pre-screened. She shared that sites continue to be engaged in enrolling participants, and there is also an investigator meeting planned at ARVO where they plan to discuss issues affecting enrollment. Ms. Chiostri reported that the new goal is to complete recruitment of 90 participants by the end of June. Dr. Duncan stated that the DSMB is concerned about recruitment. Dr. Zilliox responded that it has been difficult to enroll participants, and more sites should have been used. She noted than a more realistic assumption regarding enrollment rates would have been to assume each site would accrue a maximum of 5 participants.

Dr. Wilson briefly described the workflow at the Reading Center. He explained that image files are uploaded by the sites and a grader then decides if the file is sufficient. If it is sufficient, the file goes to the reader who then completes the reading form. If the file is insufficient, the Reading Center

communicates with the site to resolve the issue. Dr. Wilson stated that the Reading Center has a single reader for each modality (SKP, GATEi, OCT, and fundus photography). The Reading Center provides the CCC with monthly transfers of data. Ms. McCormack noted that the process has been running smoothly and the CCC has been satisfied with the monthly export. Dr. Diener-West commented that she had no concerns about this process. There were no further questions for the Reading Center.

Ms. McCormack reviewed the recommendations and action items from the October 2, 2013 DSMB meeting and the January 31, 2014 quarterly report. All action items were completed. Ms. McCormack then provided a presentation of some of the masked data from the VP1 study. She reported that Dr. Diener-West's question from the quarterly report about participants being counted twice as screen failures in the Summary of Screen Failures table (Table 3) had been addressed by adding a Summary of Re-Screened Participants table (Table 4). She noted that 23 participants had been re-screened, of which 16 were randomized and 7 screen-failed twice. Ms. McCormack next presented information on recruitment and enrollment. She noted that 7 participants are currently in screening (6 mentioned by Ms. Chiostri plus 1 additional), 2 baseline visits are scheduled for May, 1 screening visit was planned for April 30, and 4 others are scheduled, 1 each in May, June, July and October. She commented that the CCC continues to work with sites to encourage recruitment. She noted that there have been issues with site staff and participant scheduling. Ms. McCormack pointed out in the Summary of Genetic Mutations (Table 14) that 46% of randomized participants have the RHO mutation, in addition to the 3 participants who have a RHO mutation along with another mutation (2 with PRPH2, 1 with R0M1).

Ms. McCormack provided a description of data on treatment exposure and compliance included in Section 3.3 of the Open Session report. She reported that 15 participants (18%) terminated study medication early, with a number of them terminating medication due to adverse events (AE). She noted that 25 participants had treatment exposure below 90% due to being non- compliant, temporarily or permanently withdrawn from study drug, and dose reductions. Professor Rothenberg inquired if the number of participants with lower treatment exposure will impact the analysis of efficacy. Ms. McCormack responded that it is not optimal, and these participants will be included in the final analysis as part of the Intent-to-Treat population. She noted that the lower treatment exposure could affect the treatment effect observed. Ms. McCormack stated that a Per-Protocol population analysis is planned which would exclude participants with low treatment exposure. The precise definition of the Per-Protocol population is still being determined.

Professor Rothenberg questioned if the AEs leading to early study medication termination are expected AEs due to VPA. Dr. Lindblad responded that the AEs leading to early study medication termination are included in the package insert for VPA. He noted that whether or not the AE leads to the participant withdrawing from study medication is dependent on the participant's tolerance. Dr. Rothenberg inquired if the AEs reported in the VP1 study were predictable and Dr. Lindblad replied that the AEs seen were predictable in any trial. Dr. Fine agreed with Dr. Lindblad.

Ms. McCormack reported that no further SAEs have occurred since the last DSMB meeting. She provided an update on the death of a participant due to a motorcycle accident. She noted that there have been 7 participants with clinically significant elevated liver function labs, 4 with clinically significant elevated pancreatic function labs, and 3 with clinically significant elevated ammonia levels.

The next DSMB meeting is scheduled on October 1, 2014 from noon to 4 pm ET in Columbia, MD.